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**Hippo signaling disruption and Akt stimulation of ovarian follicles for infertility treatment.**

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**Public Summary:**

**Scientific Abstract:**

Primary ovarian insufficiency (POI) and polycystic ovarian syndrome are ovarian diseases causing infertility. Although there is no effective treatment for POI, therapies for polycystic ovarian syndrome include ovarian wedge resection or laser drilling to induce follicle growth. Underlying mechanisms for these disruptive procedures are unclear. Here, we explored the role of the conserved Hippo signaling pathway that serves to maintain optimal size across organs and species. We found that fragmentation of murine ovaries promoted actin polymerization and disrupted ovarian Hippo signaling, leading to increased expression of downstream growth factors, promotion of follicle growth, and the generation of mature oocytes. In addition to elucidating mechanisms underlying follicle growth elicited by ovarian damage, we further demonstrated additive follicle growth when ovarian fragmentation was combined with Akt stimulator treatments. We then extended results to treatment of infertility in POI patients via disruption of Hippo signaling by fragmenting ovaries followed by Akt stimulator treatment and autografting. We successfully promoted follicle growth, retrieved mature oocytes, and performed in vitro fertilization. Following embryo transfer, a healthy baby was delivered. The ovarian fragmentation-in vitro activation approach is not only valuable for treating infertility of POI patients but could also be useful for middle-aged infertile women, cancer patients undergoing sterilizing treatments, and other conditions of diminished ovarian reserve.

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